Quinapril

℞

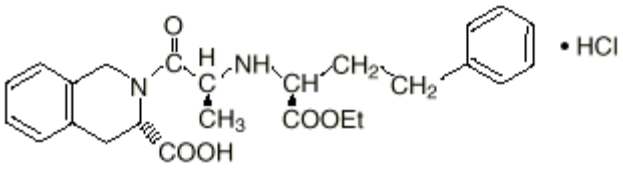
ACCUPRIL
5 mg, 10 mg and 20 mg Tablet

1.0 PHARMACOLOGIC CATEGORY

Angiotensin-Converting-Enzyme (ACE) Inhibitors

2.0 DESCRIPTION

Quinapril hydrochloride is the salt of quinapril, the ethyl ester of a non-sulfhydryl, angiotensin-converting enzyme (ACE) inhibitor, quinaprilat.
Quinapril hydrochloride is chemically described as [3S-[2[R*(R*)], 3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl] amino]-1-oxopropyl]-1, 2, 3, 4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. Its empirical formula is $C_{25}H_{30}N_2O_5$ • HCl and its structural formula is



M.W.=474.98

Quinapril hydrochloride is a white to off-white amorphous powder, freely soluble in aqueous solvents with a melting point of 108 to 115°C.

Quinapril hydrochloride (Accupril) 5 mg tablets are brown elliptical film-coated tablets with the dosage strength “5” embossed on one side, bisecting score and “PD 527” embossed on the other.

Quinapril hydrochloride (Accupril) 10 mg tablets are reddish brown triangular biconvex film-coated tablets with bisecting score on both sides and debossing “10” on one side.

Quinapril hydrochloride (Accupril) 20 mg tablets are reddish brown round film-coated tablets with the dosage strength “20” debossed on one side and bisecting score and “PD 532” debossed on the other.

3.0 FORMULATION/ COMPOSITION

Quinapril hydrochloride (Accupril) 5 mg Tablet: Each tablet contains Quinapril hydrochloride equivalent to 5 mg Quinapril Ph. Eur.

Quinapril hydrochloride (Accupril) 10 mg Tablet: Each tablet contains Quinapril hydrochloride equivalent to 10 mg Quinapril Ph. Eur.

Quinapril hydrochloride (Accupril) 20 mg Tablet: Each tablet contains Quinapril hydrochloride equivalent to 20 mg Quinapril Ph. Eur.

4.0 CLINICAL PARTICULARS

4.1. Therapeutic indications

Hypertension

Quinapril is indicated for the treatment of hypertension. Quinapril is effective as monotherapy or concomitantly with thiazide diuretics and beta-blockers in patients with hypertension.

Congestive Heart Failure

Quinapril is effective in the treatment of congestive heart failure when given concomitantly with a diuretic and/or cardiac glycoside.

4.2. Dosage and method of administration

Hypertension

Monotherapy: The recommended initial dosage of quinapril in patients not on diuretics is 10 mg or 20 mg once daily. Depending upon clinical response, the patient's dosage may be titrated (by doubling the dose) to a maintenance dosage of 20 mg/day or 40 mg/day, usually given as a single dose or may be divided in two doses. Generally, dosage adjustments should be made at intervals of 4 weeks. Long-term control is maintained in most patients with a single daily dosage regimen. Patients have been treated with dosages of quinapril up to 80 mg/day.

Concomitant Diuretics: In patients who must continue treatment with a diuretic, the initial recommended dosage of quinapril is 5 mg, which should subsequently be titrated (as described above) to the optimal response (see **section 4.5. Interaction with other medicinal products and other forms of interaction**).

Congestive Heart Failure

Quinapril is indicated as adjunctive therapy with diuretics and/or cardiac glycosides. The recommended initial dosage in patients with congestive heart failure is 5 mg once or twice daily, following which the patient should be monitored closely for symptomatic hypotension. If the initial dose of quinapril is well tolerated, patients may be titrated up to an effective dose, usually 10 mg/day to 40 mg/day given in two equally divided doses with concomitant therapy.

Use in Renal Impairment

See **section 4.4. Special warnings and precautions for use**. Kinetic data indicate that quinapril elimination is dependent on the level of renal function. The recommended initial dose of quinapril is 5 mg in patients with a creatinine clearance above 30 mL/min and 2.5 mg in patients with a creatinine clearance less than 30 mL/min. If the initial dose is well tolerated, quinapril may be administered the following day as a twice-daily regimen. In the absence of excessive hypotension or significant deterioration of renal function, the dose may be increased at weekly intervals based on clinical and hemodynamic response. Recommended starting dosages based on clinical and pharmacokinetic data from patients with renal impairment are as follows:

Creatinine Clearance (mL/min)	**Maximum Recommended Initial Dosage** (mg)
>60	10
30-60	5
10-30	2.5
<10	*

*There is insufficient experience at this time to allow for specific dosage recommendations in these patients.

Use in Elderly

Age alone does not appear to affect the efficacy or safety profile of quinapril. Therefore, the recommended initial dosage of quinapril in elderly patients is 10 mg given once daily followed by titration to the optimal response.

Use in Children

Safety and effectiveness of quinapril in pediatric patients have not been established.

4.3. Contraindications

Quinapril is contraindicated in patients who are hypersensitive to any component of this product (i.e. quinapril hydrochloride, Magnesium carbonate, Gelatin, Lactose, Crospovidone, Magnesium stearate, Hypromellose, Hydroxypropyl cellulose, Titanium dioxide, Macrogol 400, Iron oxide red and Candelilla wax) and in patients with a history of angioedema related to previous treatment with an angiotensin-converting enzyme (ACE) inhibitor.

Quinapril is contraindicated in combination with sacubitril/valsartan due to the increased risk of angioedema.

Quinapril is also contraindicated in women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraceptive measures. Quinapril should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus (see **section 4.6. Fertility, pregnancy and lactation**).

Do not administer quinapril in combination with aliskiren:

- in patients with diabetes
- in patients with moderate to severe kidney insufficiency (glomerular filtration rate [GFR] <60 mL/min/1.73 m^2)
- in patients with hyperkalemia (>5 mmol/L)
- in congestive heart failure patients who are hypotensive

Do not administer quinapril in combination with angiotensin receptor blockers or other ACE inhibitors.

4.4. Special warnings and precautions for use

Head and Neck Angioedema

Angioedema has been reported in 0.1% of patients receiving quinapril. If laryngeal stridor or angioedema of the face, tongue, or glottis occur, treatment with quinapril should be discontinued immediately; the patient should be treated appropriately in accordance with accepted medical care and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. Angioedema associated with laryngeal involvement may be fatal. Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate emergency therapy, including, but not limited to, subcutaneous adrenalin (epinephrine) solution 1:1000 (0.3 to 0.5 mL), should be promptly administered.

Black patients receiving ACE inhibitor therapy have been reported to have a higher incidence of angioedema compared to non-black patients. It should also be noted that in controlled clinical trials, ACE inhibitors have an effect on blood pressure that is less in black patients than in non-

black patients. The incidence of angioedema in black and non-black patients during quinapril therapy has been calculated in two large open-label clinical trials evaluating the effectiveness of quinapril in the management of hypertension. In one study wherein 1656 black and 10,583 non-black patients were evaluated, the incidence of angioedema, regardless of association to quinapril treatment, was 0.3% in black patients and 0.39% in non-black patients. In the other study (1443 black and 9300 non-black patients), the incidence of angioedema was 0.55% in black patients and 0.17% in non-black patients.

Patients taking a concomitant mammalian target of rapamycin (mTOR) inhibitor (e.g. temsirolimus) or a concomitant dipeptidyl peptidase-IV (DPP-IV) inhibitor (e.g. vildagliptin) therapy or a neutral endopeptidase inhibitor may be at increased risk for angioedema. Caution should be used when starting an mTOR inhibitor or a DPP-IV inhibitor or a neutral endopeptidase inhibitor in a patient already taking an ACE inhibitor.

Intestinal Angioedema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases, there was no prior history of facial angioedema, and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk for angioedema while receiving an ACE inhibitor.

Anaphylactoid Reactions

Desensitization: Patients receiving ACE inhibitors during desensitizing treatment with hymenoptera venom have sustained life-threatening anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld, but they have reappeared upon inadvertent rechallenge.

Low-density lipoprotein apheresis: Patients undergoing low-density lipoprotein (LDL) apheresis with dextran-sulfate absorption when treated concomitantly with an ACE inhibitor, have reported anaphylactoid reactions.

Hemodialysis: Clinical evidence has shown that patients hemodialyzed using certain high-flux membranes (such as polyacrylonitrile membranes) are likely to experience anaphylactoid reactions with concomitant ACE inhibitor treatment. This combination should be avoided, either by use of alternative antihypertensive drugs, or alternative membranes for hemodialysis.

Dual Blockage of the Renin-Angiotensin System

Please see section **4.5. Interaction with other medicinal products and other forms of interaction**.

Hypotension

Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with quinapril but is a possible consequence of ACE inhibitor therapy in salt/volume depleted patients such as those previously treated with diuretics, who have a dietary salt restriction, or who are on dialysis.

Patients already receiving a diuretic when quinapril is initiated can develop symptomatic hypotension. In patients receiving a diuretic, it is recommended to stop the diuretic for 2 to 3

days before starting quinapril. If blood pressure is not controlled with quinapril alone, diuretic therapy should be resumed. If it is not possible to withdraw diuretic therapy, begin quinapril at a low initial dose (see **section 4.5. Interaction with other medicinal products and other forms of interaction**).

In patients with congestive heart failure, who are at risk of excessive hypotension, quinapril therapy should be started at the recommended dose under close medical supervision; these patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of quinapril is increased.

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses; however, lower doses of quinapril or any concomitant diuretic therapy should be considered if this event occurs.

Neutropenia/Agranulocytosis

ACE inhibitors have been rarely associated with agranulocytosis and bone marrow depression in patients with uncomplicated hypertension but more frequently in patients with renal impairment, especially if they also have collagen vascular disease.

Agranulocytosis has been rarely reported during treatment with quinapril. Monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality

See **section 4.6. Fertility, pregnancy and lactation**.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with quinapril may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death (see **section 4.8. Undesirable effects**).

The half-life of quinaprilat is prolonged as creatinine clearance falls. Patients with a creatinine clearance of <60 mL/min require a lower initial dosage of quinapril (see **section 4.2. Dosage and method of administration**). These patients' dosage should be titrated upwards based upon therapeutic response, and renal function should be closely monitored, although initial studies do not indicate that quinapril produces further deterioration in renal function.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when quinapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of a diuretic and/or quinapril may be required.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy (see **section 4.8. Undesirable effects**).

Impaired Hepatic Function

Quinapril when combined with a diuretic should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. The metabolism of quinapril to quinaprilat is normally dependent upon hepatic esterase. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril.

Hyperkalemia

Patients on quinapril alone may have increased serum potassium levels. Because of the risk of further potentiating increases in serum potassium, it is advised that combination therapy with potassium-sparing diuretics or other drugs known to raise serum potassium levels, be initiated with caution and the patient's serum potassium levels be closely monitored (see **section 4.5. Interaction with other medicinal products and other forms of interaction**). When administered concomitantly, quinapril may reduce the hypokalemia induced by thiazide diuretics.

Hyponatremia and Syndrome of Inappropriate Anti-diuretic Hormone (SIADH)

Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatremia has been observed in some patients treated with other ACE inhibitors. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatremia.

Hypoglycemia and Diabetes

ACE inhibitors have been associated with hypoglycemia in diabetic patients on insulin or oral hypoglycemic agents; closer monitoring of diabetic patients may be required.

Cough

Cough has been reported with the use of quinapril. Characteristically, the cough is non-productive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia

Caution should be exercised when patients undergo major surgery or anesthesia since ACE inhibitors have been shown to block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension, which can be corrected by volume expansion.

Psoriasis and Aggravation of Psoriasis

Psoriasis or aggravation of psoriasis has been reported in patients receiving ACE inhibitors. Quinapril should be used with caution in patients, especially those with a medical history or family history of psoriasis. Consider discontinuation of quinapril if clinically significant psoriasis or psoriasis aggravation occurs.

Information for Patients

Pregnancy: Quinapril must not be used by women who are pregnant, intend to become pregnant, or could become pregnant and who are not using adequate contraceptive measures because of the potential of drug effects that may seriously injure or even cause fatality to a

developing fetus (see **section 4.3. Contraindications** and **section 4.4. Special warnings and precautions for use**, Fetal/Neonatal Morbidity and Mortality).

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of quinapril. Patients should be advised that if any sign or symptom suggesting angioedema occurs (i.e., swelling of the face, extremities, eyes, lips, tongue; difficulty in swallowing or breathing), they should immediately stop taking quinapril and consult with their physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of quinapril therapy. If syncope occurs, the patients should be told not to take the drug until they have consulted with their physician.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, or dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion, such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g. sore throat, fever), as this could be a sign of neutropenia.

Surgery/Anesthesia: Patients planning to undergo surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

NOTE: As with many other drugs, certain advice to patients being treated with quinapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

4.5. Interaction with other medicinal products and other forms of interaction

Tetracycline and Other Drugs That Interact with Magnesium

Administration of tetracycline with quinapril reduced the absorption of tetracycline by approximately 28% to 37% in subjects. Decreased absorption is due to the presence of magnesium carbonate as an excipient in the quinapril formulation. This interaction should be considered if co-prescribing quinapril and tetracycline.

Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy due to the sodium-losing effect of these agents. Quinapril and lithium should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Non-steroidal Anti-inflammatory Agents Including Selective Cyclooxygenase-2 Inhibitors

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors, with ACE inhibitors, including quinapril, may result in deterioration of renal function, including possible acute renal

failure. These effects are usually reversible. Monitor renal function periodically in patients receiving quinapril and NSAID therapy.

The antihypertensive effect of ACE inhibitors, including quinapril, may be attenuated by NSAIDs.

Other Drugs Known to Cause Angioedema

Please see section **4.4. Special warnings and precautions for use**.

Other Agents

No clinically important pharmacokinetic interactions occurred when quinapril was used concomitantly with propranolol, hydrochlorothiazide, digoxin or cimetidine.

The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril co-administration twice daily.

Co-administration of multiple 10 mg doses of atorvastatin with 80 mg quinapril resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

Concomitant Diuretic Therapy

Patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with quinapril. Hypotensive effects after the first dose of quinapril may be minimized by discontinuing the diuretic a few days prior to initiation of therapy. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced. In patients in whom a diuretic is continued, medical supervision should be provided for up to 2 hours after the initial dosage of quinapril (see **section 4.4. Special warnings and precautions for use** and section **4.2. Dosage and method of administration**).

Agents Increasing Serum Potassium

Quinapril is an ACE inhibitor capable of lowering aldosterone levels, which in turn can result in potassium retention. Therefore, concomitant therapy of quinapril with potassium-sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, potassium-containing salt substitutes or other drugs known to raise serum potassium levels should be used with caution and with appropriate monitoring of serum potassium (see **section 4.4. Special warnings and precautions for use**). In patients who are elderly or have compromised renal function, co-administration of an ACE inhibitor with sulfamethoxazole/trimethoprim has been associated with severe hyperkalemia, which is thought to be due to trimethoprim. Quinapril and trimethoprim-containing products should therefore, be co-administered with caution and with appropriate monitoring of serum potassium.

Dual Blockage of the Renin-Angiotensin System

Dual blockage of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on quinapril and other agents that affect the RAS.

Do not administer quinapril in combination with aliskiren in patients with diabetes, in patients with moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2), in patients with hyperkalemia (>5 mmol/L) or in congestive heart failure patients who are hypotensive (see **section 4.3. Contraindications**).

Do not administer quinapril in combination with angiotensin receptor blockers or other ACE inhibitors in diabetic patients with end organ damage, in patients with moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2), in patients with hyperkalemia (>5 mmol/L), or in congestive heart failure patients who are hypotensive (see **section 4.3. Contraindications**).

4.6. Fertility, pregnancy and lactation

Pregnancy

Quinapril is contraindicated in pregnancy (see **section 4.3. Contraindications**). ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Should a woman become pregnant while receiving quinapril, the drug should be discontinued.

Infants exposed to ACE inhibitors during pregnancy may be at increased risk for malformations of the cardiovascular system and central nervous system. There have also been reports of prematurity, hypotension, renal system disorders (including renal failure), skull hypoplasia, oligohydramnios, limb contractures, craniofacial deformities, hypoplastic lung development, intrauterine growth retardation, patent ductus arteriosus, fetal death, and/or death in the newborn in association with the maternal use of ACE inhibitors. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants who may have been exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion.

Nursing Mothers

ACE inhibitors, including quinapril, are secreted in human milk to a limited extent. Because of this, caution should be exercised when quinapril is given to a nursing mother.

4.7. Effects on ability to drive and use machines

The ability to engage in activities, such as operating machinery or operating a motor vehicle may be impaired, especially when initiating quinapril therapy.

4.8. Undesirable effects

Quinapril has been evaluated for safety in 4960 subjects and patients and was well tolerated. Of these, 3203 patients including 655 elderly patients participated in controlled clinical trials. Quinapril has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient in nature. The most frequent clinical adverse reactions in controlled trials were headache (7.2%), dizziness (5.5%), cough (3.9%), fatigue (3.5%), rhinitis (3.2%), nausea and/or vomiting (2.8%), and myalgia (2.2%). It should be noted that, characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy.

Discontinuation of therapy because of adverse events was required in 5.3% of the patients treated with quinapril in controlled clinical trials.

Adverse experiences occurring in 1% or more of the 3203 patients in controlled clinical trials who were treated with quinapril with or without a concomitant diuretic are shown below. Incidence of adverse experiences in the subset of 655 patients aged 65 years and older is

given for comparison. A subset of the 2005 patients in controlled clinical trials who were treated with quinapril monotherapy for hypertension is also presented.

Percent of Patients in Controlled Studies				
	Quinapril ± %	Diuretic	Monotherapy	Placebo
Adverse Event	Total N = 3203*	≥65 years N = 655	% N = 2005**	% N = 579**
Headache	7.2	4.0	8.1	16.9
Dizziness	5.5	6.6	4.1	4.3
Coughing	3.9	4.1	3.2	1.4
Fatigue	3.5	3.5	3.2	2.1
Nausea and/or vomiting	2.8	3.8	2.3	2.6
Myalgia	2.2	1.2	1.7	3.3
Diarrhea	2.0	2.4	1.9	1.0
Chest Pain	2.0	1.8	1.2	1.9
Abdominal Pain	1.9	1.8	2.0	2.2
Dyspepsia	1.6	1.2	1.9	1.2
Dyspnea	1.5	2.3	0.9	0.5
Back Pain	1.4	1.7	1.3	1.0
Pharyngitis	1.3	0.5	1.5	1.9
Insomnia	1.3	0.8	1.3	0.7
Hypotension	1.1	1.8	1.0	0.0
Paresthesia	1.1	0.9	1.0	0.9
*Includes 454 patients treated for congestive heart failure **Includes patients treated for hypertension only				

Clinical adverse experiences probably, possibly, or definitely related, or of uncertain relationship to therapy occurring in 0.5% to <1.0% (except as noted) of the patients treated with quinapril (with or without concomitant diuretic) in controlled or uncontrolled trials and less frequent events seen in clinical trials or post-marketing experience (indicated by *) included:

Blood and lymphatic system disorders: hemolytic anemia,* thrombocytopenia*

Immune system disorders: anaphylactoid reaction*

Psychiatric disorders: depression, nervousness

Nervous system disorders: somnolence, vertigo

Eye disorders: amblyopia

Cardiac disorders: angina pectoris, palpitations, tachycardia

Vascular disorders: postural hypotension,* syncope,* vasodilatation

Gastrointestinal disorders: dry mouth or throat, flatulence, pancreatitis*

Skin and subcutaneous tissue disorders: alopecia,* exfoliative dermatitis,* increased perspiration, pemphigus,* photosensitivity reaction,* pruritus, rash, psoriasis*

Musculoskeletal and connective tissue disorders: arthralgia

Renal and urinary disorders: urinary tract infection (see **section 4.4. Special warnings and precautions for use)**

Reproductive system and breast disorders: impotence

Congenital, familial, and genetic disorders: See **section 4.3. Contraindications** and **section 4.6. Fertility, pregnancy and lactation**

General disorders and administration site conditions: edema (peripheral and generalized)

Rare events: angioedema* (0.1%) was reported in patients receiving quinapril (see **section 4.3. Contraindications** and **section 4.4. Special warnings and precautions for use**). While rarely seen with quinapril, eosinophilic pneumonitis* and hepatitis have been reported with other ACE inhibitors.

Clinical Laboratory Test Findings

Agranulocytosis and neutropenia have been reported rarely (see **section 4.4. Special warnings and precautions for use**).

Hyperkalemia: See **section 4.3. Contraindications and section 4.4. Special warnings and precautions for use**.

Hyponatremia: See **section 4.4. Special warnings and precautions for use.**

Creatinine and Blood Urea Nitrogen: Increases, greater than 1.25 times the upper limit of normal, in serum creatinine and blood urea nitrogen were observed in 2% of the patients treated with quinapril alone. These increases often reversed on continued therapy (see **section 4.4. Special warnings and precautions for use**).

4.9 Overdose and Treatment

The oral LD_{50} of quinapril in mice and rats ranges from 1440 mg/kg to 4280 mg/kg.

No specific information is available on the treatment of overdosage with quinapril. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion.

Treatment is symptomatic and supportive consistent with established medical care.

Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Quinapril hydrochloride is the salt of quinapril, the ethyl ester of a nonsulfhydryl ACE inhibitor, quinaprilat.

Administration of 10 mg to 40 mg of quinapril to patients with mild to moderate hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate. Antihypertensive activity commences within 1 hour with peak effects usually achieved by 2 to 4 hours after dosing. Achievement of maximum blood pressure-lowering effects may require 2 weeks of therapy in some patients. At the recommended doses, antihypertensive effects are

maintained in most patients throughout the 24-hour dosing interval and continued during long-term therapy.

Hemodynamic assessments in patients with hypertension have indicated that blood pressure reduction produced by quinapril is accompanied by a reduction in total peripheral resistance and renal vascular resistance with little or no change in heart rate, cardiac index, renal blood flow, GFR or filtration fraction.

Concomitant therapy with thiazide-type diuretics and/or the addition of beta-blocker therapy enhances the antihypertensive effects of quinapril, giving a blood pressure-lowering effect greater than that seen with either agent alone.

Therapeutic effects appear to be the same for elderly (≥65 years of age) and younger adult patients given the same daily dosages, with no increase in the incidence of adverse events in elderly patients.

Quinapril administration to patients with congestive heart failure reduces peripheral vascular resistance, mean arterial pressure, systolic and diastolic blood pressure, and pulmonary capillary wedge pressure, and increases cardiac output.

In 149 patients undergoing elective coronary bypass surgery, treatment with quinapril 40 mg reduced the incidence of post-operative ischemic events compared to placebo during a 1-year follow-up.

In patients with documented coronary artery disease (CAD) but without manifest hypertension or heart failure, quinapril improves abnormal endothelial function measured in coronary and brachial arteries.

Quinapril enhances endothelial function by mechanisms leading to increased availability of nitric oxide. Endothelial dysfunction is considered an important underlying pathophysiological mechanism in CAD. The clinical significance of improving endothelial function has not been established.

Mechanism of Action

Quinapril is rapidly deesterified to quinaprilat (quinapril diacid, the principal metabolite), which, in human studies, is a potent ACE inhibitor. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor angiotensin II, which is involved in vascular control and function through many different mechanisms, including stimulation of aldosterone secretion by the adrenal cortex. The mode of action of quinapril in humans and animals is to inhibit circulating and tissue ACE activity, thereby decreasing vasopressor activity and aldosterone secretion. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA).

While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, quinapril exerts antihypertensive actions even in patients with low renin hypertension. Quinapril monotherapy was an effective antihypertensive in all races studied, although it was somewhat less effective in blacks (usually a predominantly low renin group) than in non-blacks. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator; whether increased levels of bradykinin play a role in the therapeutic effect of quinapril remains to be elucidated.

In animal studies, the antihypertensive effect of quinapril outlasts its inhibitory effect on circulating ACE, whereas tissue ACE inhibition more closely correlates with the duration of its antihypertensive effects.

ACE inhibitors, including quinapril, may enhance insulin sensitivity.

5.2 Pharmacokinetic Properties

Following oral administration, peak plasma quinapril concentrations are observed within 1 hour. Based on the recovery of quinapril and its metabolites in the urine, the extent of absorption is approximately 60%. Thirty-eight percent of orally administered quinapril is systemically available as quinaprilat. Quinapril has an apparent half-life in plasma of approximately 1 hour. Peak plasma quinaprilat concentrations are observed approximately 2 hours following an oral dose of quinapril. Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of approximately 3 hours. Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins.

In patients with renal insufficiency, the apparent elimination half-life of quinaprilat increases as creatinine clearance decreases. Pharmacokinetic studies in patients with end-stage renal disease on chronic hemodialysis or continuous ambulatory peritoneal dialysis indicate that dialysis has little effect on the elimination of quinapril and quinaprilat. There is a linear correlation between plasma quinaprilat clearance and creatinine clearance. The elimination of quinaprilat is also reduced in elderly patients (≥65 years) and correlates well with their level of renal function (see **section 4.2. Dosage and method of administration**).

Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

Pharmacokinetics in the Elderly

Elderly patients exhibited increased AUC and peak levels for quinaprilat compared to values in younger patients; this appeared to be related to decreased renal function rather than to age itself. In controlled and uncontrolled studies where 21% of patients were 65 years or older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

5.3. Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50-60 times the maximum human daily dose, respectively) for 104 weeks. Neither quinapril nor quinaprilat was mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister-chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro* chromosome aberration with V79 cultured lung cells, and an in vivo cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at dose levels up to 100 mg/kg/day (60 times the maximum daily human dose).

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 times the maximum daily human dose), despite maternal toxicity at 150 mg/kg/day. Offspring body weights were reduced in rats treated late in gestation and during lactation with doses of 25 mg/kg/day or more. Quinapril was not teratogenic in rabbits; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at doses as low as 0.5 mg/kg/day and 1 mg/kg/day, respectively.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf Life

For expiry date, please see outer package.

6.2 Storage conditions

Store at temperatures not exceeding 25°C.

6.3 Availability

Quinapril hydrochloride (Accupril) 5 mg tablets are available as aluminum packs of 14's in boxes of 56's.

Quinapril hydrochloride (Accupril) 10 mg tablets are available as aluminum packs of 14's in boxes of 56's.

Quinapril hydrochloride (Accupril) 20 mg tablets are available as aluminum packs of 14's in boxes of 56's.

7.0 FDA REGISTRATION NUMBER

5 mg film-coated tablet : DRP - 2002
10 mg film-coated tablet : DRP - 3124
20 mg film-coated tablet : DRP - 3104

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

5 mg film-coated tablet : 26 March 1990
10 mg film-coated tablet : 26 March 1990
20 mg film-coated tablet : 26 March 1990

KEEP OUT OF REACH OF CHILDREN.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
Pfizer Manufacturing Deutschland GmbH
Betriebsstatte Freiburg, Mooswaldallee 1
79090 Freiburg, Germany

Marketing Authorization Holder:
Pfizer, Inc.
19F-20F, 8 Rockwell Building,
Hidalgo Drive, Rockwell Center, Poblacion,
Makati City 1210 Metro Manila, Philippines

Under the authority of PFIZER INC., New York, N.Y., U.S.A.

Revision No.: 9.1
Revision Date: 23 March 2023
Reference: CDS ver. 13/Alignment with CPR
Reference Date: 18 May 2022